Official Title: A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies

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STATISTICAL ANALYSIS PLAN

INCAGN 1876-201

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies

IND Number:	[redacted]
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Protocol Version:	**Protocol Amendment 2 dated 22 AUG 2017**
CRF Approval Date:	**02 MAY 2017**
SAP Version:	**Original**
SAP Author:	[redacted]**, Ph.D.** [redacted]**, Biostatistics**
Date of Plan:	**05 DEC 2017**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
1876	INCAGN01876
[redacted]	[redacted]
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0-\infty)}$	AUC from time zero (predose) extrapolated to infinite time
$AUC_{(0-\tau)}$	AUC from time zero (predose) to time of last observed quantifiable concentration within a subject across all treatments
BOR	best overall response
CI	confidence interval
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
IL	interleukin
Ipi	ipilimumab
irAE	immune-related AE
JTc	corrected JT interval
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST v1.1	modified Response Evaluation Criteria in Solid Tumors version 1.1
MSI	microsatellite instability
MTD	maximum tolerated dose
NE	not evaluable

Abbreviation	Term
Nivo	nivolumab
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
[redacted]	[redacted]
PoS	probability of success
PR	partial response
PT	preferred term
Q2W	every 2 weeks
QTcF	QT interval corrected using the Fridericia formula
QRS	QRS is the combination of three of the graphical deflections on an ECG. It is usually the most central and most visually obvious part of the tracing. It corresponds to the depolarization of the right and left ventricles of the human heart.
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
RR	RR is the interval from the beginning of a QRS complex to the beginning of the next QRS complex
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMT	Safety Management Team
SOC	system organ class
T	time of last observed quantifiable concentration
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 1/2 open-label, nonrandomized, multicenter study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. This study will be conducted in 2 phases. Phase 1 will use a 3 + 3 + 3 design to determine the MTD, or PAD, for INCAGN01876 when given in combination with immune therapies in subjects with advanced or metastatic tumors. Phase 2 of the study will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies in subjects with advanced or metastatic endometrial cancer, gastric cancer, and SCCHN. Section 1 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCAGN01876.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCAGN 1876-201 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee.

[redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCAGN 1876-201 Protocol Amendment 2 dated 22 AUG 2017 and CRFs approved 02 MAY 2017. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives

2.2.1. Primary Objectives

Phase 1

- To evaluate the safety, tolerability, and DLTs of INCAGN01876 in combination with immune therapies and to define the RP2D(s) of INCAGN01876 when given in combination with immune therapies.

Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing ORR per RECIST v1.1.

2.2.2. Secondary Objectives

Phase 1 and Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing ORR, DOR, duration of disease control, and PFS per RECIST v1.1 and mRECIST v1.1.

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies with respect to 1-year and 2-year OS.
- To evaluate the safety and tolerability of INCAGN01876 when given in combination with immune therapies.

[redacted]

2.3. Study Endpoints

2.3.1. Primary Endpoints

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.
- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1.

2.3.2. Secondary Endpoints

- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- DOR, defined as the time from the earliest date of disease response (CR or PR) until earliest date of disease progression or death due to any cause, if occurring sooner than progression, will be determined by investigator assessment of radiographic disease assessment per RECIST v1.1 and mRECIST v1.1.
- DCR, defined as the percentage of subjects having CR, PR, or SD, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- Duration of disease control (CR, PR, and SD) as measured from first report of SD or better until disease progression or death from any cause, if occurring sooner than

progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1.

- PFS, defined as the time from the start of combination therapy until the earliest date of disease progression or death due to any cause, if occurring sooner than progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- OS determined from the start of combination therapy until death due to any cause. Survival analyses will occur at 1-year, 2-years, and at the end of the study.
- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.

[redacted]

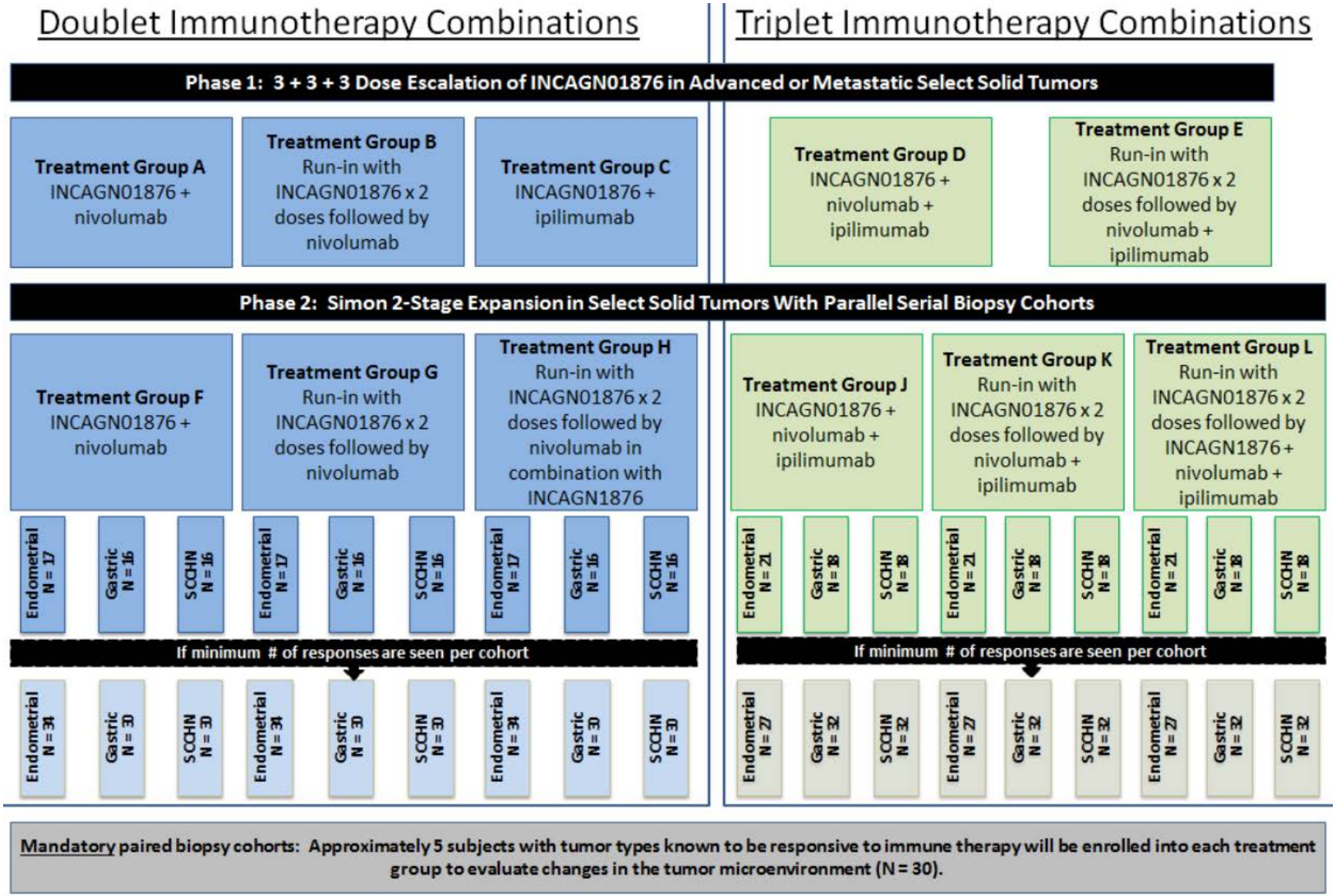
3. STUDY DESIGN

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. The MTD or PAD of INCAGN01876 when given in combination with immune therapies will be determined in Phase 1 of the study. In Phase 1, subjects will receive escalating doses of INCAGN01876 on Day 1 of each cycle. Phases 1 and 2 of the study will utilize 14-day cycles. The study will be conducted in 2 phases:

- **Phase 1 – Dose Escalation** will consist of a 3 + 3 + 3 dose escalation to determine the MTD or PAD, defined as a dose that provides a maximal biochemical effect or an increase in biomarkers of immune activity of INCAGN01876 when given in combination with immune therapies. Phase 1 will begin with 3 doublet treatment groups evaluating the MTD or PAD of INCAGN01876 plus nivolumab (Treatment Groups A and B) and the MTD or PAD of INCAGN01876 plus ipilimumab (Treatment Group C), which will be explored in parallel. Dose escalation of the triplet immune therapy combinations (Treatment Groups D and E) of INCAGN01876 plus nivolumab plus ipilimumab will begin enrolling once all of the applicable doublet combinations have cleared 3 INCAGN01876 dose levels or the MTD or PAD of INCAGN01876 has been determined (whichever occurs first). Alternative dosing schedules will be explored in Phase 1, including concurrent dosing (Treatment Group A for the doublet combination of INCAGN01876 plus nivolumab and Treatment Group D for the triplet combination) and run-in with INCAGN01876 × 2 doses followed by immune therapy(ies) (Treatment Group B for the doublet combination of INCAGN01876 plus nivolumab and Treatment Group E for the triplet combination).
- **Phase 2 – Dose Expansion** will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies in subjects with advanced or metastatic endometrial cancer, gastric cancer, and SCCHN. Alternative dosing schedules will be explored in Phase 2, including concurrent dosing (Treatment Group F for the doublet combination of INCAGN01876 plus nivolumab and Treatment Group J for the triplet combination), run-in with INCAGN01876 × 2 doses followed by immune therapy(ies) (Treatment Group G for the doublet and Treatment Group K for the triplet), and run-in with INCAGN01876 × 2 doses followed by concurrent dosing with immune therapy(ies) (Treatment Group H for the doublet and Treatment Group L for the triplet).

See Figure 1 for overall study design.

Figure 1: Overall Study Design



3.1. Dose Escalation

In Phase 1 of the study, the MTD is defined as 1 dose level below that at which ≥ one-third of subjects in a particular cohort have DLTs. The PAD is defined as a dose that provides a maximal biochemical effect or an increase in biomarkers of immune activity of INCAGN01876 when given in combination with immune therapies.

A DLT will be defined as the occurrence of any toxicity, with the exception of events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity; the list of toxicities that will be designated as DLTs are provided in Table 6 of the Protocol.

In the dose escalation part of the study, a 3 + 3 + 3 design will be used to determine the MTD or PAD of INCAGN01876 when given in combination with immune therapies.

Phase 1 will begin with 3 doublet treatment groups A, B, and C, which will be explored in parallel. Dose escalation of the triplet treatment groups D and E will be explored in parallel and will begin enrolling once all of the applicable doublet combinations have cleared 3 INCAGN01876 dose levels or the MTD or PAD of INCAGN01876 has been determined (whichever occurs first). The starting dose of INCAGN01876 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. For example, if 3 mg/kg of INCAGN01876 is safe in the doublet combinations with both nivolumab and ipilimumab, then the starting dose in the triplet will be 0.3 mg/kg. If the MTD of INCAGN01876 is 1 mg/kg in the doublet combinations, then the starting dose of INCAGN01876 for the triplet immune therapy combination will be 0.1 mg/kg. If there are different MTDs of INCAGN01876 with nivolumab and ipilimumab, then the starting dose of the triplet will be 2 dose levels below the lowest MTD in the doublet.

Based on safety data from monotherapy (INCAGN 1876-101), a minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with INCAGN01876 Dose Cohort 3 (1.0 mg/kg; starting dose).

The first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for the specified DLT observation period before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experiences a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 evaluable subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 evaluable subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If ≥ 2 of 3, 3 of 6, or 3 of 9 evaluable subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD. If only 3 evaluable subjects were treated at the MTD or PAD, then a minimum of 3 additional evaluable subjects will be enrolled before this dose is administered in Phase 2 of the study.

Additional subjects will be enrolled in a dose cohort to achieve the minimum of 3 evaluable subjects. Depending on the treatment group, a subject must receive at least 2 doses of the cohort-specified dose of INCAGN01876, 2 doses of nivolumab, and 1 dose of ipilimumab, or must have had a DLT during the DLT observation period, to be considered evaluable. Subjects who dropout for reasons other than a DLT (eg, events clearly associated with the underlying

disease, disease progression, concomitant medication, or comorbidity), during the DLT observation period will result in the subject being nonevaluable and the subject being replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. The doses of INCAGN01876 to be evaluated in each treatment group are summarized in Table 1.

Table 1: INCAGN01876 Dose Levels and Cohorts

Cohort	Dose of INCAGN01876
3 (Starting Dose)	**1.0 mg/kg**[a]
4	3.0 mg/kg
5	5.0 mg/kg
6	10.0 mg/kg

[a] Based on safety data from the monotherapy (INCAGN 1876-101), the starting dose of INCAGN01876 was determined to be 1.0 mg/kg.

3.2. Phase 2 – Dose Expansion

Enrollment in Phase 2 will begin when the MTD or PAD of INCAGN01876 for a given treatment group in Phase 1 has been determined. Phase 2 of the study will further evaluate the safety, tolerability, efficacy, [redacted] and pharmacologic activity of the immune therapy combinations in subjects with advanced or metastatic endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), and SCCHN. Additional tumor-specific cohorts may be added, by protocol amendment, based on emerging data.

Biopsy cohorts will be added at specific institutions for each treatment group (F, G, H, J, K, and L), where serial mandatory pretreatment and on-treatment biopsies will be collected [redacted] Approximately 5 subjects who have tumor lesions that are amenable to percutaneous biopsy will be enrolled in each biopsy cohort. The biopsy-specific cohorts will be limited to subjects with cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), hepatocellular carcinoma, melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, MSI-high colorectal cancer, non–small cell lung cancer, ovarian cancer, SCCHN, small cell lung cancer, renal cell carcinoma, triple-negative breast cancer, and urothelial carcinoma.

In Phase 2, a Simon 2-stage design will be run for a cohort of endometrial, gastric, and SCCHN subjects within a given doublet or triplet drug expansion cohort to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. The design parameters for the individual Simon 2-stage designs are determined by historical response rates and will result in different sample sizes and different futility rules, depending on the historical response rate for the tumor type and treatment combination. The planned Simon 2-stage designs are summarized in Table 2. The same Simon 2-stage design parameters will be used for alternative dosing sequences in the same tumor type and treatment combination. For example, the gastric cohorts in Treatment Groups F, G, and H will all use the same Simon 2-stage parameters.

Table 2: Planned Simon 2-Stage Designs for Phase 2

Indication	Treatment Groups	r_1	n_1	r	n_2	n	p_0	p_1
SCCHN	F, G, H	3	16	10	30	46	15%	35%
Gastric	F, G, H	3	16	10	30	46	15%	35%
Endometrial	F, G, H	4	17	14	34	51	20%	40%
SCHHN	J, K, L	5	18	17	32	50	25%	45%
Gastric	J, K, L	5	18	17	32	50	25%	45%
Endometrial	J, K, L	7	21	19	27	48	30%	50%

- r_1: if r_1 or fewer responses are observed during Stage 1, the study cohort is stopped early for futility.
- n_1: number of subjects initially enrolled in Stage 1.
- n_2: number of subjects enrolled in Stage 2.
- r: if r or fewer responses are observed by the end of Stage 2, then no further investigation of the drug combination is warranted in the selected tumor type and dosing schedule.
- n: total number of subjects.
- p_0: insufficient response rate.
- p_1: target response rate.

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 to 5 INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment in that treatment group will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule. All AEs, regardless of the time of occurrence on study, may be considered for DLT determination purposes.

3.3. Control of Type I Error

For the primary efficacy endpoints, the 1-sided Type I error will be controlled at 0.05 for each individual cohort expansion. Note that this level of significance does not account for the multiple expansion cohorts. For other endpoints, CIs will be reported at a 95% confidence level.

During the Phase 1 portion of the study, telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions. An internal DMC will be assembled to monitor safety data and

study conduct on a regular and ongoing basis during the Phase 2 portion of the study. See Section 9 for details regarding the interim analyses conducted in this study.

3.4. Sample Size Considerations

3.4.1. Sample Size in Phase 1

The primary objective in Phase 1 of the study is to determine the MTD or PAD of INCAGN01876 when given in combination with immune therapies. The total number of subjects will depend on the number of dose levels tested in each treatment group before the MTD or PAD is established. Approximately 90 (3 subjects per dose level for 6 dose levels in 5 treatment groups) to 270 (9 subjects per dose level for 6 dose levels in 5 treatment groups) evaluable subjects. Dose escalation will follow the 3 + 3 + 3 design algorithm. Based on this algorithm, a minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 3 (1 mg/kg; starting dose) and a maximum of 9 evaluable subjects will be enrolled in each cohort. The probability of declaring a dose as safe for various DLT rates in the 3 + 3 + 3 is summarized in Table 3.

Table 3: Probability of Dose Escalation by DLT Rate for 3 + 3 + 3 Design

True DLT Rate	Probability of Declaring Dose Cohort as Safe
10%	94.9%
20%	78.4%
30%	56.1%
40%	35.0%
50%	18.9%
60%	8.8%

For example, if the true DLT rate is 50% at a given dose level, there is an 18.9% chance that the dose would be escalated. Further, if the true DLT rate is 20%, there is a 78.4% chance that the dose would be escalated. If the MTD is not determined at the highest dose level tested during the study, then the MTD is at or above the highest dose level. The MTD is below the lowest dose level of INCAGN01876 if Cohort 1 is not well-tolerated. The PAD may be used in lieu of the MTD and/or prescribed doses may need to be altered in order to determine the MTD.

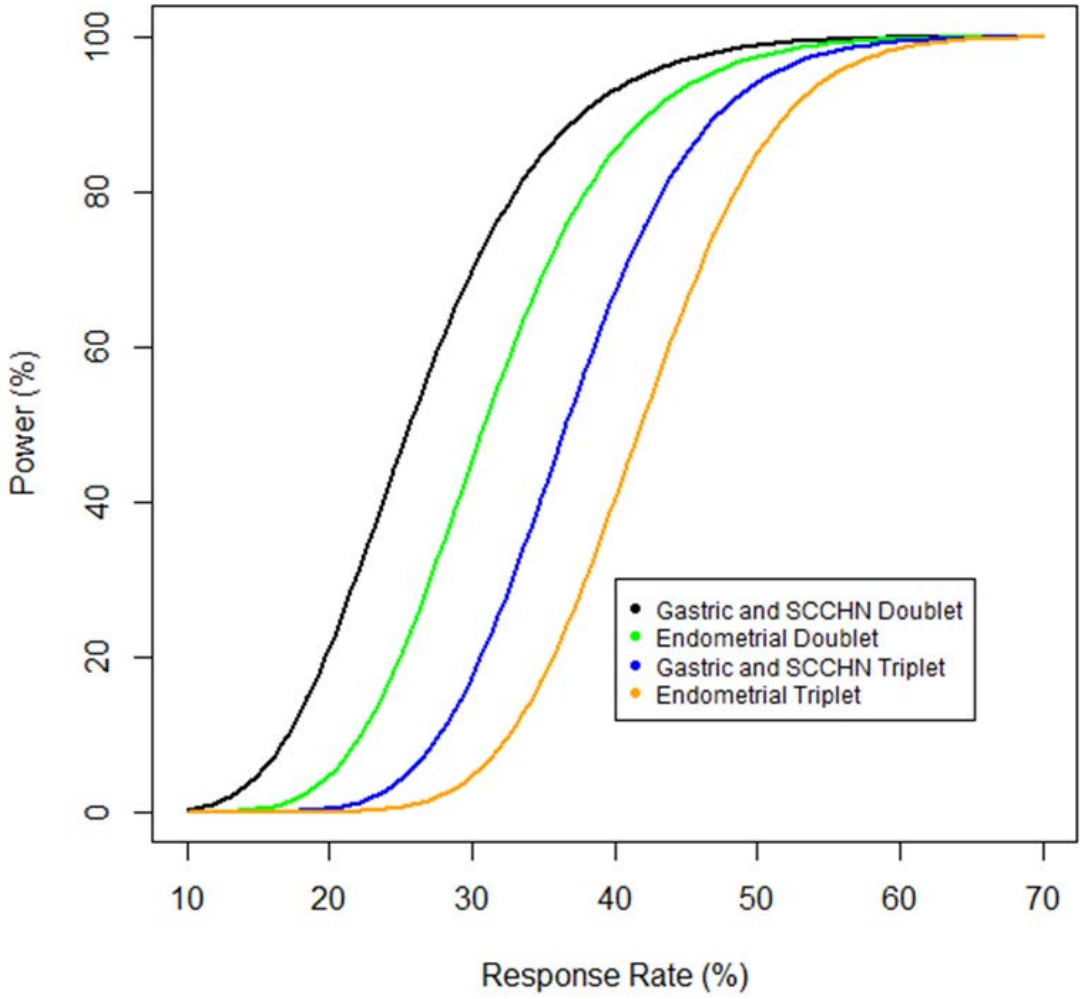
3.4.2. Sample Size in Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, [redacted] and pharmacologic activity of the recommended dose of INCAGN01876 in combination with immune therapies as part of doublet and triplet drug expansion cohorts. In Phase 2, a Simon 2-stage design will be run for each tumor type within a given doublet or triplet drug expansion cohort.

The sample size for each tumor type within a given doublet or triplet expansion cohort will be guided by the Simon 2-stage design (Simon 1989). As discussed in Section 3.3, the Simon 2-stage designs conducted for each tumor type within each doublet or triplet expansion cohort have design parameters that are determined by historical response rates and will have different sample sizes and different futility rules, depending on the historical response rate.

In order to determine whether the target response rate (p_1) is likely, an initial number of evaluable subjects (n_1 subjects) treated at the MTD or PAD and schedule of INCAGN01876 within the corresponding doublet or triplet expansion cohort will be enrolled in a cohort (Stage 1). If there are r_1 or fewer responses in the cohort, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate, and no more subjects will be enrolled in that tumor type in Stage 2. In the cohorts in which greater than r_1 responses are observed among the Stage 1 subjects, n_2 additional evaluable subjects will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if $\leq r$ subjects have responded among the n evaluable subjects, the doublet or triplet schedule will be declared nonpromising for that cohort. In other words, after the study is finished, if there is a sufficient number of responses in the 2 stages combined, the study doublet or triplet is considered promising; otherwise it is considered nonpromising. The detailed calculations for each tumor type-specific doublet and triplet cohort are based on a 1-sided Type I error of 0.05 and power of 85%. The individual $p0$ and $p1$ values for the tumor types within doublet or triplet expansion cohorts are listed in Table 2. Table 2 shows that there are 4 unique Simon 2-Stage designs: the Simon 2-stage designs for gastric and SCCHN within the INCAGN01876 + nivolumab cohorts use the same assumptions as the Simon 2-stage designs for gastric and SCCHN within the INCAGN01876 + nivolumab + ipilimumab cohorts. Figure 2 shows the power to reject the null hypothesis under various response rates for the 4 unique Simon 2-stage designs, in which each line of the figure represents the power for a unique Simon 2-stage design.

Figure 2: Power and Type 1 Error for Various Response Rates for 4 Unique Simon 2-Stage Designs



For the biopsy cohorts, if a predictive biomarker with 33% prevalence is associated with response, n = 5 subjects provides an 86.5% probability of enrolling at least 1 subject with the predictive biomarker in the cohort in question.

3.5. Schedule of Assessments

Refer to Protocol Amendment 2 dated 22 AUG 2017 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study treatment (INCAGN01876, nivolumab, or ipilimumab) is administered to the subjects.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of -1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCAGN01876, nivolumab, or ipilimumab, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Last Available Value

The last available value is the last nonmissing measurement obtained after starting INCAGN01876, nivolumab, or ipilimumab and within 60 days after the last dose of INCAGN01876, nivolumab or ipilimumab.

4.1.5. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial disease diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the subject discontinued treatment.
- Otherwise, the date that the subject discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial death date will be imputed as follows:

- If mmyyyy for the last contact date = mmyyyy for the death date, then the death date will be set to the day after the last contact date.
- If mmyyyy for the last contact date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.6. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of INCAGN01876, nivolumab, or ipilimumab is administered. One treatment cycle consists of 14 days. The first cycle of therapy is defined as the period beginning with the first dose of INCAGN01876, nivolumab, or ipilimumab and ending the earlier of the following 1) 14 calendar days (inclusive later) or 2) permanent discontinuation of 1 or more of the following: INCAGN01876, nivolumab, and ipilimumab. Subsequent cycles have Day 1 as the corresponding visit date associated with the corresponding cycle. Note that dosing of ipilimumab is once every 6 weeks.

In Phase 2, subjects in Treatment Groups F and H will be administered INCAGN01876 at the RP2D determined by Treatment Group A along with nivolumab and subjects in Treatment Group G will be administered INCAGN01876 at the RP2D determined by Treatment Group B along with nivolumab. Subjects in Treatment Groups J and L will be administered INCAGN01876 at the RP2D determined by Treatment Group D along with nivolumab and ipilimumab and subjects in Treatment Groups K will be administered INCAGN01876 at the RP2D determined by Treatment Group E along with nivolumab and ipilimumab.

Subjects will continue to receive INCAGN01876, nivolumab, and ipilimumab as defined in the protocol as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal.

4.2. Variable Definitions

4.2.1. Variables to Be Derived Only If Not Provided on Case Report Form

The following variables will only be calculated if not reported on the CRF:

- Subject age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form (ICF), using the following formula:

  Age = integer part of (date of informed consent – date of birth + 1) / 365.25

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCAGN01876, nivolumab, or ipilimumab.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCAGN01876, nivolumab, or ipilimumab and is ongoing throughout the study or ends on/after the date of first study treatment administration.
- On/after the date of first administration of INCAGN01876, nivolumab, or ipilimumab and is ongoing or ends during the course of study treatment.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCAGN01876, nivolumab, or ipilimumab. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

This is a Phase 1/2, open-label, nonrandomized, multicenter, dose-escalation study. In Phase 1, because the starting dose of INCAGN01876 is 1.0 mg/kg in Cohort 3, up to 4 doses of INCAGN01876 will be tested. Data will be summarized by treatment group and by dose level.

Dose escalation of the triplet immune therapy combinations will begin enrolling once all of the applicable doublet combinations have cleared 3 INCAGN01876 dose levels (see Table 1) or the MTD or PAD of INCAGN01876 has been determined (whichever occurs first). The starting dose of INCAGN01876 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. The triplet immune therapy combinations will be explored in parallel as outlined in Figure 1.

- Treatment Group A:
  - INCAGN01876 1.0 mg/kg + nivolumab 240 mg
  - INCAGN01876 3.0 mg/kg + nivolumab 240 mg
  - INCAGN01876 5.0 mg/kg + nivolumab 240 mg
  - INCAGN01876 10.0 mg/kg + nivolumab 240 mg
- Treatment Group B
  - 1.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 240 mg
  - 3.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 240 mg
  - 5.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 240 mg
  - 10.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 240 mg
- Treatment Group C
  - INCAGN01876 1.0 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 3.0 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 5.0 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 10.0 mg/kg + ipilimumab 1 mg/kg

- Treatment Group D
  - INCAGN01876 1.0 mg/kg + nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 3.0 mg/kg + nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 5.0 mg/kg + nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - INCAGN01876 10.0 mg/kg + nivolumab 3 mg/kg + ipilimumab 1 mg/kg
- Treatment Group E
  - 1.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - 3.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - 5.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - 10.0 mg/kg run-in with INCAGN01876 × 2 doses followed by nivolumab 3 mg/kg + ipilimumab 1 mg/kg

In Phase 2, endometrial, gastric, SCCHN subjects and a separate biopsy cohort will be enrolled in each treatment group. Data will be summarized by treatment group and tumor type–specific cohort.

- Treatment Group F: RP2D from Treatment Group A INCAGN01876 + nivolumab 240 mg
  - Cohort 1: Endometrial
  - Cohort 2: Gastric
  - Cohort 3: SCCHN
  - Cohort 4: Biopsy
- Treatment Group G: RP2D from Treatment Group B INCAGN01876 run-in Q2W × 2 doses followed by nivolumab 240 mg Q2W
  - Cohort 1: Endometrial
  - Cohort 2: Gastric
  - Cohort 3: SCCHN
  - Cohort 4: Biopsy
- Treatment Group H: RP2D from Treatment Group A INCAGN01876 run-in Q2W × 2 doses followed by nivolumab 240 mg Q2W + INCAGN01876 Q2W
  - Cohort 1: Endometrial
  - Cohort 2: Gastric

  - Cohort 3: SCCHN
  - Cohort 4: Biopsy
- Treatment Group J: RP2D from Treatment Group D INCAGN01876 + nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
  - Cohort 1: Endometrial
  - Cohort 2: Gastric
  - Cohort 3: SCCHN
  - Cohort 4: Biopsy
- Treatment Group K: RP2D from Treatment Group E INCAGN01876 run-in Q2W × 2 doses followed by nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
  - Cohort 1: Endometrial
  - Cohort 2: Gastric
  - Cohort 3: SCCHN
  - Cohort 4: Biopsy
- Treatment Group L: RP2D from Treatment Group D INCAGN01876 run-in Q2W × 2 doses followed by INCAGN01876 Q2W + nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
  - Cohort 1: Endometrial
  - Cohort 2: Gastric
  - Cohort 3: SCCHN
  - Cohort 4: Biopsy

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS includes all subjects enrolled in the study who received at least 1 dose of INCAGN01876, nivolumab, or ipilimumab. The FAS will be used for the summary of demographics, baseline characteristics, subject disposition, safety, study treatment administration, and analyses of all efficacy data.

- **Phase 1 FAS Population**

  The Phase 1 FAS population includes all subjects in the FAS population who are enrolled in the Phase 1 portion of the study and received at least 1 dose of INCAGN01876, nivolumab, or ipilimumab.

- **Phase 1 FAS INCAGN01876 Population**

  The Phase 1 FAS population includes all subjects in the FAS population who are enrolled in the Phase 1 portion of the study and received at least 1 dose of INCAGN01876.

- **Phase 1 FAS Weighted Nivolumab Population**

  The Phase 1 FAS weighted nivolumab population includes all subjects in the FAS population who are enrolled in the Phase 1 portion of the study and received at least 1 dose of nivolumab administered in mg/kg. This includes subjects enrolled into Treatment Groups D and E.

- **Phase 1 FAS Fixed Nivolumab Population**

  The Phase 1 FAS fixed nivolumab population includes all subjects in the FAS population who are enrolled in the Phase 1 portion of the study and received at least 1 dose of nivolumab administered in mg. This includes subjects enrolled into Treatment Groups A and B.

- **Phase 1 FAS Ipilimumab Population**

  The Phase 1 FAS ipilimumab population includes all subjects in the FAS population who are enrolled in the Phase 1 portion of the study and received at least 1 dose of ipilimumab.

- **Phase 2 FAS Population**

  The Phase 2 FAS population includes all subjects in the FAS population enrolled in Phase 2 of the study who received at least 1 dose of INCAGN01876, nivolumab, or ipilimumab.

  Specific analysis populations to be used for evaluating the Simon 2-stage efficacy rules include the following subgroups:

  – Treatment Group F adenocarcinoma of the endometrium
  – Treatment Group F with gastric cancer
  – Treatment Group F with SCCHN cancer
  – Treatment Group G with adenocarcinoma of the endometrium
  – Treatment Group G with gastric cancer
  – Treatment Group G with SCCHN cancer
  – Treatment Group H with adenocarcinoma of the endometrium
  – Treatment Group H with gastric cancer
  – Treatment Group H with SCCHN cancer
  – Treatment Group J with adenocarcinoma of the endometrium
  – Treatment Group J with gastric cancer
  – Treatment Group J with SCCHN cancer

- Treatment Group K with adenocarcinoma of the endometrium
- Treatment Group K with gastric cancer
- Treatment Group K with SCCHN cancer
- Treatment Group L with adenocarcinoma of the endometrium
- Treatment Group L with gastric cancer
- Treatment Group L with SCCHN cancer

Table summaries, unless otherwise indicated, will be provided by treatment group and tumor type–specific cohort.

- **Phase 2 FAS INCAGN01876 Population**

  The Phase 2 FAS population includes all subjects in the FAS population who are enrolled in the Phase 2 portion of the study and received at least 1 dose of INCAGN01876.

- **Phase 2 FAS Weighted Nivolumab Population**

  The Phase 2 FAS weighted nivolumab population includes all subjects in the FAS population who are enrolled in the Phase 2 portion of the study and received at least 1 dose of nivolumab administered in mg/kg. This includes subjects enrolled into Treatment Groups J, K, and L.

- **Phase 2 FAS Fixed Nivolumab Population**

  The Phase 2 fixed FAS nivolumab population includes all subjects in the FAS population who are enrolled in the Phase 2 portion of the study and received at least 1 dose of nivolumab administered in mg. This includes subjects enrolled into Treatment Groups F, G, and H.

- **Phase 2 FAS Ipilimumab Population**

  The Phase 2 FAS ipilimumab population includes all subjects enrolled in the Phase 2 portion of the study who received at least 1 dose of ipilimumab.

5.3.2. Response Evaluable Populations

5.3.2.1. Phase 1 Response Evaluable Population

The Phase 1 response evaluable population includes all subjects enrolled in Phase 1 of the study who have received at least 1 dose of INCAGN01876, nivolumab, or ipilimumab; completed a baseline scan; and met at least 1 of the following criteria:

- ≥ 1 postbaseline scan OR
- The subject has been on the study for a minimum of 64 days of follow-up OR
- The subject has discontinued from treatment.

5.3.2.2. Phase 2 Response Evaluable Population

The Phase 2 response evaluable population includes all subjects enrolled in Phase 2 of the study who have received at least 1 dose of INCAGN01876, nivolumab, or ipilimumab; completed a baseline scan; and met at least 1 of the following criteria:

- ≥ 1 postbaseline scan OR
- The subject has been on the study for a minimum of 64 days of follow-up OR
- The subject has discontinued from treatment.

[redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of data displays. Sample data displays will be provided in a separate document.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics

The following demographics will be summarized for the Phase 1 FAS population by treatment group and dose level and for the Phase 2 FAS population by treatment group and tumor type: age, sex, race, ethnicity, and ECOG performance status.

6.1.2. Baseline Disease Characteristics and Disease History

For each type of tumor, primary tumor histology, time from initial diagnosis in months, stage at initial diagnosis, current stage of disease, current site of disease, and tumor markers will be summarized for all subjects in the Phase 1 FAS population by treatment group and dose level and Phase 2 FAS population by treatment group and tumor type.

6.1.3. Prior Therapy

Number of prior systemic cancer therapy regimens will be summarized for all subjects in the Phase 1 FAS population by treatment group and dose level and Phase 2 FAS population by treatment group and tumor type. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed by total number and by number of prior systemic cancer therapies taken for both advanced and metastatic disease.

Number of subjects who received prior radiation will be summarized for the FAS population. Radiotherapy type, body site, start and stop date, total dose, and best response will be listed.

Number of subjects who had prior surgery or surgical procedure for the malignancies under study will be summarized for the FAS population. Date and description of the surgery/procedure will be listed.

Number of subjects with prior immunotherapy and prior anti–PD-1/PD-L1 therapy will be summarized for the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. Prior immunotherapy type, start and stop date, total dose, and best response will be listed.

6.1.4. Medical History

Medical history will be summarized according to assigned treatment group by dose level for subjects in the Phase 1 FAS population and by tumor type for the Phase 2 FAS population. This summation will include the number and percentage of subjects with significant medical history for each body system/organ class as documented on the CRF.

6.2. Disposition of Subjects

The number and percentage of subjects who were enrolled, treated, completed the study, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for the Phase 1 FAS population by treatment group and dose level and for the Phase 2 population by treatment group and tumor type. The number of subjects enrolled by site will also be provided by treatment group.

6.3. Protocol Deviations and Violations

Protocol deviations and violations recorded on the CRF will be presented in the subject data listings.

6.4. Exposure

6.4.1. Exposure for INCAGN01876

For subjects in the FAS population, exposure to INCAGN01876 will be summarized descriptively as the following:

- **Total number of infusions:** Total number of infusions per subject with a nonzero dose of INCAGN01876.
- **Dose administered per cycle (mg/kg):** The actual dose administered in mg/kg per cycle.
- **Total dose administered (mg/kg):** The total cumulative, actual dose administered (in mg/kg) across cycles for each subject will be determined according to the following calculation:
  - For an infusion i, let C_i be the concentration (in mg/mL) of INCAGN01876 and V_i be the total volume administered (in mL) reported on the INCAGN01876 dosing CRF; let W be the subject's baseline weight (in kg), and N be the total number of infusions:

    Total dose administered (in mg/kg) = $\sum_{i=1}^{N} \frac{C_i \times V_i}{W}$.
- **Average dose of INCAGN01876 (mg/kg):** The average dose (mg/kg) will be the total dose administered (in mg/kg) divided by the total number of infusions.
- **Dose administered per cycle (mg):** The actual dose administered in mg per cycle.
- **Total dose administered (mg):** Total cumulative, actual dose administered (in mg) across cycles for each subject will be determined according to the following calculation:
  - For an infusion i, let C_i, V_i, and N be defined as above:

    Total dose administered (in mg) = $\sum_{i=1}^{N} C_i \times V_i$.
- **Average dose of INCAGN01876 (mg):** The average dose (mg) will be the total dose administered (in mg) divided by the total number of infusions.

6.4.2. Exposure for Nivolumab

For subjects in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type, exposure to nivolumab will be summarized descriptively as the following:

- **Total number of infusions:** Number of infusions of nivolumab (mg) for a subject will be the number of administered, nonzero infusions of nivolumab (mg) recorded on the Nivolumab Dosing CRF.
- **Dose administered per cycle of nivolumab (mg):** The actual dose administered in mg per cycle. Dose administered per cycle of nivolumab (mg) will only be summarized for subjects in the Phase 1 FAS Fixed Nivolumab Population and Phase 2 FAS Fixed Nivolumab Population.
- **Average dose of nivolumab (mg):** The average dose of nivolumab (mg) will be the sum of the doses of nivolumab recorded (mg) on the Nivolumab Dosing CRF divided by the number of infusions of nivolumab (mg). Average dose of nivolumab (mg) will only be summarized for subjects in the Phase 1 FAS Fixed Nivolumab Population and Phase 2 FAS Fixed Nivolumab Population.
- **Dose administered per cycle of nivolumab (mg/kg):** The actual dose administered in mg/kg per cycle. Dose administered per cycle of nivolumab (mg/kg) will only be summarized for subjects in the Phase 1 FAS Weighted Nivolumab Population and Phase 2 FAS Weighted Nivolumab Population.
- **Average dose of nivolumab (mg/kg):** The average dose of nivolumab (mg/kg) will be the sum of the doses of nivolumab recorded (mg/kg) on the Nivolumab Dosing CRF divided by the number of infusions of nivolumab (mg/kg). Average dose of nivolumab (mg/kg) will only be summarized for subjects in the Phase 1 FAS Weighted Nivolumab Population and Phase 2 FAS Weighted Nivolumab Population.

6.4.3. Exposure for Ipilimumab

- **Total number of infusions:** Number of doses of ipilimumab for a subject will be the number of administered, nonzero infusions of ipilimumab recorded on the Ipilimumab Dosing CRF.
- **Dose administered per cycle of ipilimumab (mg/kg):** The actual dose administered in mg/kg per cycle.
- **Average dose of ipilimumab (mg/kg):** The average dose of ipilimumab (mg/kg) will be the sum of the doses of ipilimumab recorded on the Ipilimumab Dosing CRF divided by the number of infusions of ipilimumab.

6.5. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary March 2017 version and summarized by WHO drug class and WHO drug term by treatment group and dose level in the Phase 1 FAS population and by treatment group and tumor type in the Phase 2 FAS population. Results will be summarized as number and percentage of subjects with prior and concomitant medications by preferred term and WHO drug class.

7. EFFICACY

Sample data displays are provided in a separate document.

7.1. General Considerations

The primary efficacy endpoint for this study is ORR per RECIST v1.1 assessed in the Phase 2 Response Evaluable Population. Secondary efficacy endpoints of this study include ORR, DOR, duration of disease control, DCR, and PFS by investigator assessment based on RECIST v1.1 and mRECIST v1.1 as well as OS assessed at 1 year and 2 years.

7.2. Efficacy Hypotheses

Each Simon 2-stage design will test the null hypothesis that the true ORR is less than or equal to the clinically insignificant response rate p_0 against the alternative hypothesis that the true ORR is equal to the target rate of p_1. For each Simon 2-stage design, the value for p_0 is determined by a historical response rate. The same values for $p_0$and $p_1$will be used for alternative dosing sequences in the same tumor type and treatment combination. For example, the gastric cohorts in Treatment Groups F, G, and H will all use the same value for p_0 and p_1.

7.3. Analysis of the Primary and Secondary Efficacy Parameters

7.3.1. Response Criteria

Overall disease status will be categorized using RECIST v1.1 and mRECIST v1.1. Subjects will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions.

7.3.2. Objective Response Rate and Best Overall Response

7.3.2.1. Confirmed ORR and Confirmed BOR by RECIST v1.1

Per RECIST v1.1, in nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses are not the result of measurement error. Therefore, a subject is defined as a confirmed objective responder if the subject has an overall response of CR or PR at any postbaseline visit that is confirmed at a subsequent timepoint at least 4 weeks later, before the first occurrence of PD. Confirmed objective responders will be assessed based on RECIST v1.1.

Confirmed ORR is defined as the proportion of subjects with confirmed overall responses. Confirmed ORR will be estimated with 95% CIs. Confidence intervals will be based on the method for Simon 2-stage CIs of response rates outlined in Koyama and Chen (2008).

Confirmed ORR will be summarized by treatment group and tumor type as primary endpoint for the Phase 2 response evaluable population.

In general, confirmed BOR is the best response recorded postbaseline before and including the first PD, in the order of CR, PR, SD, PD and NE, in which CR and PR must be confirmed at a subsequent timepoint at least 4 weeks after the CR or PR is observed. Responses of CR, PR, or SD after the first assessment of PD will not be considered. In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 49 (56 – 7) days. Subjects who fail to meet this criterion will have confirmed BOR of PD if the next available assessment indicates PD or NE if there is no additional assessment available.

Under RECIST v1.1, if radiologic imaging shows CR or PR, a tumor assessment should be repeated at a minimum of 4 weeks to confirm the response in order to claim the CR or PR as the confirmed BOR. If there is no second CR or PR tumor assessment, the CR or PR will be unconfirmed. Table 4 lists the scenarios of responses that can occur after an unconfirmed CR or PR and provides a rule for determining the confirmed BOR in each scenario. A sensitivity analysis for the ORR, in which BOR is determined using unconfirmed PR and CR, is detailed in Section 7.3.2.2.

For determination of confirmed BOR, confirmatory scans with a response of NE will be subsequently followed by another scan at a minimum of 4 weeks. For example, in the case of PR at the first timepoint followed by NE at a subsequent timepoint, if a third scan shows a PR, then the confirmed BOR will be PR. There will be no third confirmatory scans performed for a loss of response. For example, if a response of PR at the first timepoint is followed by a response of SD or PD at a subsequent timepoint, the confirmed BOR will be determined using the rules in Table 4.

Table 4: Derivation of Confirmed Best Overall Response

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Confirmed Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease status PD at that point (since disease must have reappeared after CR). Confirmed BOR would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had a PR, not a CR at the first timepoint. Under these circumstances, the original CR should be changed to a PR, and the confirmed BOR is PR.

For subjects with measurable disease at baseline, the RECIST v1.1 assessment criteria presented in Table 5 can be used to determine the overall disease status at a given timepoint based on the target lesion, nontarget lesion, and new lesion assessment.

Table 5: RECIST Evaluation Criteria for Overall Response: Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.2.1.1. Subgroup Analyses for Confirmed Best Overall Response Under RECIST v1.1 in Phase 2

Subgroups will be formed based on the following subject characteristics and baseline variables for those subjects enrolled in Phase 2 of the study whose data are available.

- PD-L1 expression within tumor type: high, negative/low, unknown
- Number of prior therapies for advanced and metastatic disease within tumor type
- Subjects with > 1 postbaseline scan within tumor type
- Tumor-type disease characteristics including the following:
  - Endometrium – MSI status (high, low, stable, unknown)
  - SCCHN – human papilloma virus status (positive vs negative)

7.3.2.2. Unconfirmed ORR and Unconfirmed BOR by RECIST v1.1 – Sensitivity and Supportive Analyses for Confirmed ORR and Confirmed BOR by RECIST v1.1

A sensitivity analysis for the ORR assessed under RECIST v1.1 will be performed using unconfirmed CRs and PRs. The unconfirmed BOR is defined as the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. For this definition, responses of CR and PR do not need to be confirmed at a subsequent timepoint. In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 49 (56 – 7) days. Subjects who fail to meet this criterion will have BOR of PD if the next available assessment indicates PD or NE if there is no additional assessment available.

Unconfirmed ORR will be summarized by treatment group and tumor type as a sensitivity analysis for the primary endpoint ORR for the Phase 2 Response Evaluable Population and as a sensitivity analysis for the secondary endpoint ORR for the Phase 1 Response Evaluable Population.

7.3.2.2.1. Subgroup Analyses for Unconfirmed Best Overall Response by RECIST v1.1 in Phase 1

For the sensitivity analysis for unconfirmed BOR, subgroups will be formed based on the following subject characteristics and baseline variables for those subjects enrolled in Phase 1 of the study whose data are available.

- Prior treatment with an anti–PD-1/PD-L1 therapy within tumor type: Yes/No

7.3.2.3. Confirmed ORR and Confirmed BOR by mRECIST v1.1

Under mRECIST v1.1, if radiologic imaging shows CR or PR, a tumor assessment should be repeated at a minimum of 4 weeks to confirm the response in order to claim the CR or PR as the confirmed BOR. If there is no second CR or PR tumor assessment, the CR or PR will be unconfirmed. Table 4 lists the scenarios that can occur after an unconfirmed CR or PR in and provides a rule for determining the confirmed BOR in each scenario. A sensitivity analysis for the ORR assessed under mRECIST v1.1, in which BOR is determined using unconfirmed PR and CR, is detailed in Section 7.3.2.4.

The mRECIST v1.1 instrument was adapted from RECIST v1.1 to include criteria that accounts for new lesions that can occur in immuno-oncology subjects before the occurrence of an SD, PR, or CR. Under mRECIST v1.1, if radiologic imaging shows PD, tumor assessment should be repeated at a minimum of 4 weeks but not more than 6 weeks later to confirm the progression. If there is no second PD tumor assessment in the 4- to 6-week follow-up time, the PD will be defined as unconfirmed. Table 6 lists the scenarios that can occur after an unconfirmed PD in at least 4 weeks and no more than 6 weeks and provides rules for determining whether or not the unconfirmed PD will be counted as an event in the corresponding scenario.

Table 6: Rules for Determining PD Event Status After an Unconfirmed PD Under mRECIST v1.1

Event Occurring After Unconfirmed PD in the Confirmation Window (4-6 weeks)	PD Event Status
Subject had end of study/end of treatment or started new anticancer therapy.	PD will be confirmed as a PD.
Subject had a confirmed PD.	PD will be confirmed as a PD.
Subject had a CR, PR, SD, or NE.	PD will not be considered as a PD and counted as corresponding CR, PR, SD, or NE for the second timepoint only.

Confirmed ORR by mRECIST v1.1 will be summarized by treatment group and tumor type for the Phase 2 response evaluable population.

7.3.2.4. Unconfirmed ORR and Unconfirmed BOR by mRECIST v1.1 – Sensitivity and Supportive Analyses for Confirmed ORR and Confirmed BOR by mRECIST v1.1

A sensitivity analysis for the ORR assessed under mRECIST v1.1 will be performed using unconfirmed CRs and PRs. The unconfirmed BOR is defined as the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD and NE. For this definition, responses of CR and PR do not need to be confirmed at a subsequent timepoint. In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 49 (56 – 7) days. Subjects who fail to meet this criterion will have confirmed BOR of PD if the next available assessment indicates PD or NE if there is no additional assessment available.

Unconfirmed ORR as assessed by mRECIST v1.1 will be summarized by treatment group and dose level for the Phase 1 response evaluable population and by treatment group and tumor type for the Phase 2 response evaluable population.

7.3.3. Duration of Response

Duration of response will be assessed with RECIST v1.1 and mRECIST v1.1 criteria.

Censoring of DOR will follow the same algorithm as the censoring of PFS (as described in Section 7.3.7). Kaplan-Meier curves for DOR will be presented by cohort-specific tumor types. The KM estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982). A swim plot for DOR will be generated under both RECIST v1.1 and mRECIST v1.1 criteria.

Duration of response as assessed by RECIST v1.1 and mRECIST v1.1 will be summarized by treatment group and dose level for the Phase 1 response evaluable population and by treatment group and tumor type for the Phase 2 response evaluable population.

7.3.3.1. Duration of Response by RECIST v1.1

Under RECIST v1.1, for unconfirmed objective responders, DOR is defined as the time from the first overall response contributing to an unconfirmed objective response (CR or PR) to the earlier of the subject's death from any cause or first assessment of PD.

7.3.3.2. Duration of Response by mRECIST v1.1

Under mRECIST v1.1, for unconfirmed objective responders, DOR is the time from the first unconfirmed overall response contributing to an unconfirmed objective response (CR or PR) to the earlier of the subject's death from any cause or first confirmed assessment of PD. Note that the criteria for the assessment of PD in DOR are the same with ORR, which are presented in Section 7.3.2.3.

7.3.4. Duration of Disease Control and Disease Control Rate

Duration of disease control (CR, PR, and SD) is defined as the time from the first report of SD or better until disease progression or death from any cause, if occurring sooner than progression, as determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1. Note that the criteria for the assessment of PD in duration of disease control are the same with ORR, which are presented in Section 7.3.2.3.

The duration of disease control will be estimated with 95% CIs overall and by treatment group. Confidence intervals will be calculated based on the exact method for binomial distributions. Swim plots for duration of disease control will be generated separately for RECIST v1.1 and mRECIST v1.1 criteria.

Disease control rate, defined as the proportion of subjects who have disease control (CR, PR, or SD), as per RECIST v1.1 and mRECIST v1.1 will be summarized. For the determination of DCR, response of CR and PR do not need to be confirmed at a subsequent timepoint. In the case of SD, measurements must meet the SD criteria at least after the date of first dose at a minimum of 49 (56 – 7) days. Subjects who fail to meet this criterion will have confirmed BOR of PD if the next available assessment indicated PD or NE if there is no additional assessment available. Disease control rate will be estimated with 95% CIs.

Duration of disease control and DCR as assessed per RECIST v1.1 and mRECIST v1.1 will be summarized by treatment group and dose level for the Phase 1 response evaluable population and by treatment group and tumor type for the Phase 2 response evaluable population.

7.3.5. Largest Percentage Reduction in Sum of Diameters of Target Lesions

For each subject in the FAS population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percentage change from baseline, defined as the largest decrease in target lesion size for each subject, will be summarized descriptively, and a waterfall plot of the best percentage change will be generated.

Per RECIST criteria, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.

7.3.6. Percentage Change in Sum of Diameters of Target Lesions Over Time

For each subject in the FAS population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The percentage change in sum of diameter of target lesions over time will be listed and a spider plot will be generated.

7.3.7. Progression-Free Survival

Progression-free survival is defined as the length of time between the baseline visit (Day 1) and the earlier of death or PD as assessed by RECIST v1.1 and mRECIST v1.1. Date of death will be determined using the Death Report CRF.

Censoring for PFS will follow the algorithm outlined in Table 7 which is based on the FDA – Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2007).

Kaplan-Meier curves for PFS will be presented by cohort-specific tumor types. The KM estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using the Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982).

Table 7: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of Day 1
No valid postbaseline response assessments	Censored	Date of Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment. (Date of PD assessment if the new anticancer treatment started after PD.)
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after more than 1 missed assessment	Censored	Date of last valid radiologic assessment (not NE and not missing) before death

NE = not evaluable.

7.3.7.1. Progression-Free Survival by RECIST v1.1

Under RECIST v1.1, PFS is defined as the length of time between the baseline visit (Day 1) and the earlier of death or first assessment of PD as assessed by RECIST v1.1.

7.3.7.2. Progression-Free Survival by mRECIST v1.1

Under mRECIST v1.1, PFS is defined as the length of time between the baseline visit (Day 1) and the earlier of death or first confirmed assessment of PD (as described in Section 7.3.2.3 Table 6).

7.3.8. Overall Survival

Overall survival is defined as the interval between Cycle 1 Day 1 and the date of death due to any cause. Date of death will be determined using the Death Report, the Survival Follow-Up, and the Subject Status CRFs. Subjects who are lost-to-follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the subject was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit and the date the subject was last known alive from the Survival Follow-Up and Subject Status CRFs.

Kaplan-Meier time to event curves will be presented by treatment groups. Median survival will be estimated using the KM method. Kaplan-Meier estimates of 1-year and 2-year survival probabilities will be provided. Confidence intervals for median survival time will be calculated using the method of Brookmeyer and Crowley (1982).

[redacted]

8. SAFETY AND TOLERABILITY

Sample data displays are provided in a separate document.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few subjects.

Unless otherwise stated, table summaries will be limited to AEs occurring after the first dose of INCAGN01876, nivolumab, or ipilimumab.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study treatment administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the National Cancer Institute CTCAE. The CTCAE version 4.03 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to INCAGN01876, nivolumab, or ipilimumab will be considered to be treatment-related AEs and will be summarized. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs will also be tabulated.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v4.03 criteria, it will be rated on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to AE. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be collected as an AE until the event resolves. Only the worst grade will be reported in AE summaries. Also, the Grade 3 or higher AEs will be reported in a listing.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Dose-Limiting Toxicities

The number of subjects with DLTs and the type of DLT will be listed by dose level and treatment group. An AE for a subject will be identified as a DLT if the event is recorded as a protocol-defined DLT on the AE CRF.

8.2.3. Maximum Tolerated Dose

The MTD, or PAD, is defined as a dose that provides a maximal biochemical effect, or an increase in biomarkers of immune activity of INCAGN01876 when given in combination with immune therapies.

- In Phase 1 of the study, the MTD will be defined as 1 dose level below that at which ≥ one-third of subjects in a particular cohort have DLTs.
- In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or higher related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment may be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule.

- All AEs, regardless of the time of occurrence on study, may be considered in DLT determination purposes.

8.2.4. Adverse Events of Special Interest or Adverse Events of Clinical Interest

8.2.4.1. Immune-Related Adverse Events

The number of subjects with irAEs and type of irAE will be listed by treatment group and dose level for the Phase 1 FAS population and by treatment group and tumor type in the Phase 2 FAS population. Adverse event terms will be reviewed periodically without respect to treatment group by the medical monitor and clinical scientist to determine which AE terms correspond to irAEs. This periodic review may also occur after database lock. The medical monitor and clinical scientist will also review investigator-reported AEs to determine whether they qualify as irAEs. For example, a rash will be counted as an irAE even if the investigator did not report it as an irAE.

8.2.4.1.1. Adverse Events Identified as Inycte MedDRA Queries

Prospectively defined Incyte MedDRA Queries will be used to conduct analyses to evaluate the safety profile. Incyte MedDRA Queries are queries constructed by Incyte based on MedDRA preferred terms identified through review of standardized MedDRA queries for clinically relevant terms. Sets of included terms will be identified and archived before database lock for the individual studies. Incyte MedDRA Queries searches are to be conducted for the following TEAEs: hemorrhage events, dizziness, weight gain, thrombotic events, urinary tract infections, herpes zoster infections, tuberculosis, hepatitis B reactivation, and infections other than those stated previously. In addition, these other infections will be analyzed by subcategories of upper respiratory tract infections, lower respiratory tract infections, skin and soft tissue infections, alimentary tract infections, other viral infections, and miscellaneous infections with each tabulated by MedDRA preferred term.

8.2.4.2. Infusion-Related Reactions

Infusion-related reactions, defined as AEs that are identified as infusion-related reaction by the investigator on the infusion-related reaction case report form, will be summarized in a table and listing. The summaries will include the treatment group, dose level, cycle number, study day, date of onset of AE, date of the associated infusion, and signs and symptoms of the infusion-related reaction.

8.2.5. Adverse Event Summaries

An overall summary of AEs by treatment group and by tumor type as applicable will include the following:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any DLTs
- Number (%) of subjects reporting any SAEs
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs

- Number (%) of subjects reporting any TEAEs related to INCAGN01876
- Number (%) of subjects reporting any TEAEs related to nivolumab
- Number (%) of subjects reporting any TEAEs related to ipilimumab
- Number (%) of subjects who temporarily interrupted INCAGN01876 because of TEAEs
- Number (%) of subjects who temporarily interrupted nivolumab because of TEAEs
- Number (%) of subjects who temporarily interrupted ipilimumab because of TEAEs
- Number (%) of subjects who permanently discontinued INCAGN01876 because of TEAEs
- Number (%) of subjects who permanently discontinued nivolumab because of TEAEs
- Number (%) of subjects who permanently discontinued ipilimumab because of TEAEs
- Number (%) of subjects with INCAGN01876 dose reductions because of TEAEs
- Number (%) of subjects who had a fatal TEAE
- Number (%) of subjects who withdrew from study because of a TEAE

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by SOC and PT
- Summary of INCAGN01876 treatment-related AEs by SOC and PT
- Summary of nivolumab treatment-related AEs by SOC and PT
- Summary of ipilimumab treatment-related AEs by SOC and PT
- Summary of Grade 3 or higher INCAGN01876 treatment-related AEs by SOC and PT
- Summary of Grade 3 or higher nivolumab treatment-related AEs by SOC and PT
- Summary of Grade 3 or higher ipilimumab treatment-related AEs by SOC and PT
- Summary of INCAGN01876 treatment-related AEs with a fatal outcome by SOC and PT
- Summary of nivolumab treatment-related AEs with a fatal outcome by SOC and PT
- Summary of ipilimumab treatment-related AEs with a fatal outcome by SOC and PT
- Summary of treatment-emergent SAEs by SOC and PT
- Summary of treatment-emergent SAEs by PT in descending order of frequency

- Summary of INCAGN01876 treatment-related SAEs by SOC and PT
- Summary of nivolumab treatment-related SAEs by SOC and PT
- Summary of ipilimumab treatment-related SAEs by SOC and PT
- Summary of treatment-emergent non-SAE by SOC and PT.
- Summary of TEAEs leading to INCAGN01876 dose reduction by SOC and PT
- Summary of TEAEs leading to any dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of INCAGN01876 by SOC and PT
- Summary of treatment-emergent irAEs (investigator identified) by SOC and PT
- Summary of treatment-emergent irAEs (sponsor identified) by SOC and PT
- Summary of treatment-emergent irAEs (investigator identified) by SOC, PT, and maximum severity
- Summary of Grade 3 or higher treatment-emergent irAEs (investigator identified) by SOC and PT
- Life table estimate of time to first Grade 3 or higher TEAEs
- Summary of TEAEs leading to death by SOC and PT
- Summary of infusion reactions

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined using the nonmissing values collected before the first dose, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

All test results and associated normal ranges from local laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and

associated normal ranges from local laboratories will be converted to SI units. For the limited number of cases where the associated normal ranges from a local laboratory cannot be obtained despite due diligence, if query is unsuccessful at resolving the issue and analysis is mandatory then the clinical scientist and medical monitor can provide a suitable normal range to be used in determining CTC grading and flags for above and below normal.

When there are multiple laboratory nonmissing values for a subject's particular test at a scheduled visit, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries (Table 8).

Table 8: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, line graphs and box-and-whisker plots will be provided for hemoglobin, platelet counts, white blood cells, and neutrophils.

For test results that will be summarized with available normal ranges, the number and percentage of subjects with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary will be produced for each test for the safety population. The denominator for the percentage calculation will use the number of subjects in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the treatment period.

In cases where differentials of hematology parameters are obtained without corresponding absolute count data, efforts will be made to investigate if the conversion to an absolute value will lead to additional abnormalities. This will be discussed with the clinical team regarding appropriate documentation and action.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 9. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change > 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 9: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

8.5. Electrocardiograms

Twelve-lead ECGs including heart rate, PR, QRS, QT, QTcF, QTcB, JTc, and RR intervals will be obtained for each subject at the screening, end of treatment, and safety follow-up visits during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of INCAGN01876, nivolumab, or ipilimumab.

Criteria for clinically notable ECG abnormalities are defined in Table 10. Subjects exhibiting clinically notable ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for subjects with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

Table 10: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9. INTERIM ANALYSES

9.1. Overview of Interim Analyses

9.1.1. Interim Analyses for Safety

There will be no planned, formal interim analyses for the Phase 1 dose escalation portion of the study. The review of accrued clinical data will be conducted by Incyte and provided to study investigators via teleconferences at the end of Phase 1 of the study. Based on review of the most current safety data, the sponsor (in consultation with the study investigators and using the dose-escalation/de-escalation rules) will determine if and at what dose additional subjects should be treated in the study.

A DMC will be charged with evaluating interim safety results. The DMC will be comprised of members who are internal to the sponsor but not members of the study team. The DMC members will include a medical monitor who will serve as the DMC chair and meeting facilitator, the head of biostatistics or a designee, the head of regulatory affairs or a designee, and the study medical monitor who will be a nonvoting member. The DMC will meet at least every 6 months to review the rate of DLTs and irAEs in each treatment group and the overall safety of the subjects treated with INCAGN01876, nivolumab, and ipilimumab. Additional operational details of the interim analyses, including TFLs provided to the DMC, will be provided in the DMC Charter. Additional safety analyses may be performed at the discretion of the DMC chair.

Formal quarterly safety reviews will be conducted by the SMT to review safety data with the obligation to hold an SMT meeting on a quarterly basis. Per the Data Monitoring Charter, the DMC is obligated to meet at least every 6 months starting after the first 10 subjects have been dosed to review safety data with key tables, listings, and figures for review specified in the Data Monitoring Charter. During Phase 2, the study team will review efficacy and safety data every 6 months, with the key tables, listings, and figures for review also specified in the Data Monitoring Charter.

9.1.2. Interim Analyses for Futility

9.1.2.1. Simon 2-Stage Futility Rules

An interim analysis of efficacy will be conducted in Phase 2 by applying the Simon 2-stage design for each tumor within a given treatment group. During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled, and if r_1 or fewer responses (Table 2) are observed by the Week 16 assessment, then the cohort will be discontinued. To be counted as evaluable for the calculation in Stage 1, subjects must have discontinued from the study, reached the Week 16 assessment, or had at least 2 scans. As discussed in Section 3.2, the Simon 2-stage designs conducted for each tumor type within each treatment group have design parameters that are determined by historical response rates and will have different sample sizes and futility results depending on the historical response rate.

As an example, the probability of early termination for Stage 1 in the SCCHN tumor cohort for the doublet combination of INCAGN01876 and nivolumab in Treatment Groups F, G, and H is

summarized in Table 11. If at least 4 responses (CR or PR) are observed in the first evaluable 16 subjects, then 30 additional evaluable subjects will be enrolled in this cohort for Stage 2.

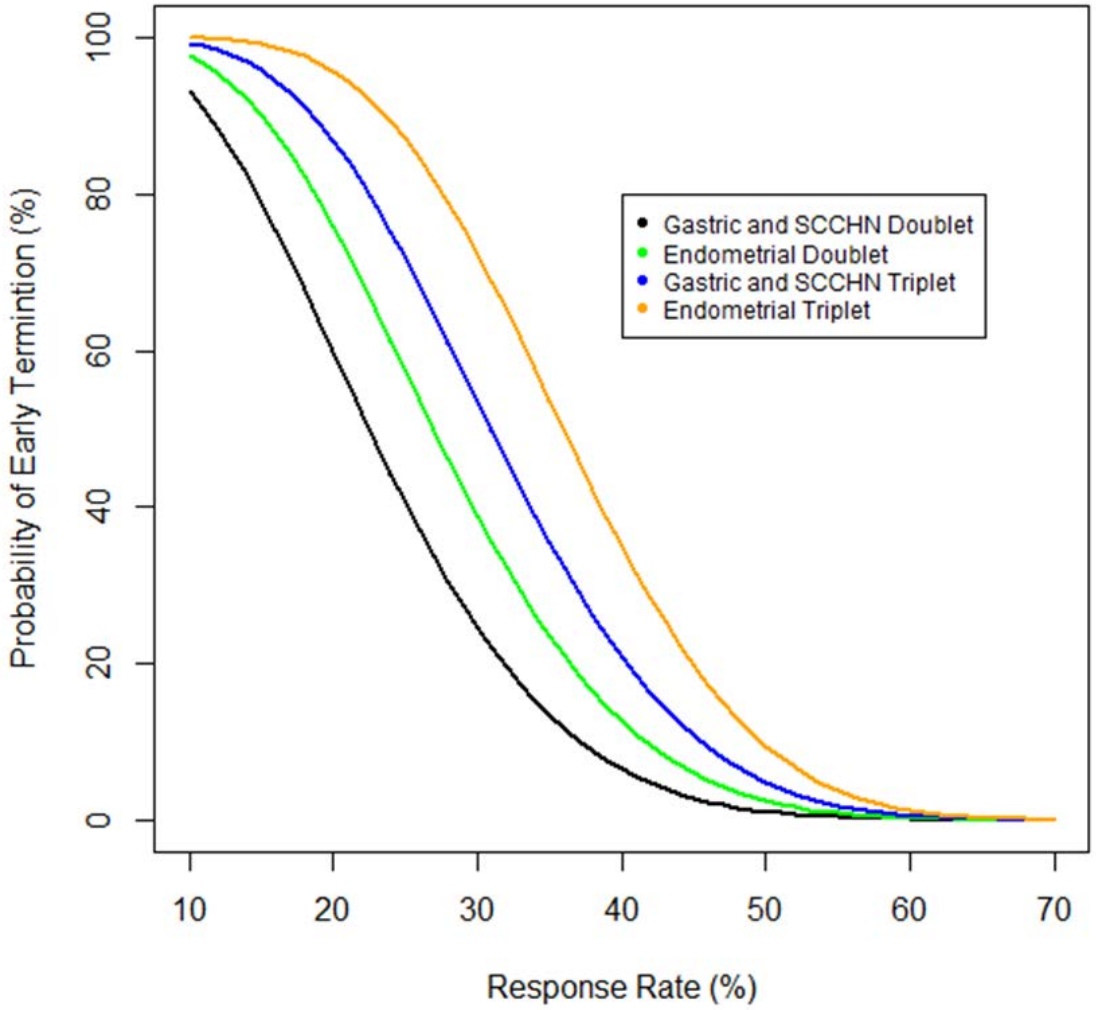
Per mRECIST v1.1, the tumor response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date that the first response was documented. Disease progression will be confirmed by a second tumor assessment in at least 4 weeks and no later than 6 weeks after the first scan indicating PD in clinically stable subjects. The first tumor assessment is conducted in the eighth week. If a CR or PR occurs after an unconfirmed PD in at least 4 weeks but no more than 6 weeks, then the tumor assessment will be counted as a corresponding CR or PR (Section 7.3.2.3).

Table 11: Probability of Early Termination of Stage 1 for Simon 2-Stage Design of SCCHN in Treatment Groups F, G, and H

True Response Rate	Probability of Early Termination at Stage 1
15%	79.0%
20%	59.8%
25%	40.5%
30%	24.6%
35%	13.4%

Table 11 provides the probabilities of early termination at the end of Simon Stage 1 for various response rates with regard to the efficacy analysis of the primary endpoint for the 4 unique Simon 2-stage designs given in Table 2. Each line in Figure 3 represents the probability of early termination for a unique Simon 2-stage design.

Figure 3: Probabilities of Early Termination for Futility at the End of Simon Stage 1 for All Simon 2-Stage Designs Based on Various Assumed Rates of Response to a Given Dose Level



9.1.2.2. Integrated Bayesian Futility Analysis

In Phase 2, individual cohorts will be closed for futility depending on the results of an integrated Bayesian analysis in which the pooling model requires a priori specification of 2 parameters: the probability of correlation among the cohorts λ and the common probability of activity in the cohorts γ. The integrated Bayesian analysis will be performed each time a subject with endometrial, gastric, or head and neck cancer enters screening. Data will be pooled from cohorts with a common dose sequencing strategy and from cohorts with a common tumor type, with λ and γ specified separately for pooling within the 2 strategies. The pooled model will produce a posterior PoS calculation for each cohort based on pooling within dose sequencing strategy, denoted by PoS1, and pooling within tumor type, denoted by PoS2. PoS is defined as the probability that the ORR for the cohort is greater than or equal to the target response rate, p_1, from the Simon 2-stage design for the cohort. The PoS calculations are adapted from Simon et al (2016).

The futility rule will stop enrollment in a tumor-sequence pair (i, j) if both $PoS1_{ij}$ or $PoS2_{ij}$ are < 20% with the possibility to re-open after more data has accrued and subsequent posterior PoS values are ≥ 20% for the tumor-sequence pair.

For the futility analyses, we specify $\lambda = 0.4$ and $\gamma=0.4$ for pooling within the tumor types and $\lambda = 0.4$ and $\gamma = 0.4$ for pooling within the sequencing strategies. In other words, a priori, the correlation between cohorts within the same tumor type and same dose sequencing strategy is assumed to be 40%, and all cohorts within the same tumor type and same dose sequencing strategy are assumed to have a 40% probability of activity.

Further details regarding the Bayesian methodology can be found in Simon et al (2016) and in the technical report in Appendix B.

Table 12 shows the dose sequencing strategy and tumor-type specific strategy for each of the 18 cohorts used for pooling in the integrated Bayesian analysis. Each cell in the table contains a number 1 to 3 representing the dose sequencing strategy and a number 4 to 9 representing the tumor type and treatment information. For pooling within dose sequencing strategy, all cohorts with a common dose sequencing number will be pooled. For pooling within the tumor types, all cohorts with a common tumor type number will be pooled. For example, for pooling within the concurrent dosing sequence, all cohorts with representative cells in the table containing a 1 will be pooled. For pooling within the tumor type strategy of gastric within INCAGN01876 + nivolumab, all cohorts with representative cells in the table containing a 5 will be pooled.

Table 12: Bayesian Pooling Strategy by Tumor Type and Sequencing Strategy

	Tumor Types Within Treatment Group		
Dosing Schedule	**Endometrial**	**Gastric**	**SCCHN**
Treatment Group F	1, 4	1, 5	1, 6
Treatment Group G	2, 4	2, 5	2, 6
Treatment Group H	3, 4	3, 5	3, 6
Treatment Group J	1, 7	1, 8	1, 9
Treatment Group K	2, 7	2, 8	2, 9
Treatment Group L	3, 7	3, 8	3, 9

1 = Concurrent dosing
2 = Run-in only dosing
3 = Run-in + concurrent dosing
4 = Endometrial within 1876 + Nivo
5 = Gastric within 1876 + Nivo
6 = SCCHN within 1876 + Nivo
7 = Endometrial within 1876 + Nivo + Ipi
8 = Gastric within 1876 + Nivo + Ipi
9 = SCCHN within 1876 + Nivo + Ipi

Table 13 provides the operating characteristics for 1000 simulated clinical trials under the global null hypothesis, under which none of the 18 cohorts are active. The table summarizes the expected sample size, expected number of false rejections, and the probability of at least 1 false positive result (family wise error rate) for the integrated Bayesian analysis. For comparison purposes, the table summarizes the expected sample size, and expected number false rejections

for 18 separate Simon 2-stage designs in which the cohorts are stopped for futility according to only the Simon 2-stage rules. In the integrated Bayesian analysis, a cohort can be stopped for futility if either PoS1 or PoS2 is not ≥ 20% or because the cohort does not meet the response rate requirement of the Simon 2-stage rule at Stage 1. From the table, under the global null hypothesis and certain enrollment assumptions, the integrated Bayesian analysis will result in 22% fewer subjects on average.

Table 13: Operating Characteristics for the Integrated Bayesian Futility Analysis Under the Global Null Hypothesis

Integrated Bayesian Analysis			18 Simon 2-Stage Designs	
Expected Sample Size	**Probability of at Least 1 False Positive**	**Expected Number of False Rejections**	**Expected Sample Size**	**Expected Number of False Rejections**
355.2	0.0876	0.104	457.2	0.9

9.2. Data Cutoff for Interim Analysis

As discussed in Section 9.1.1, the DMC will meet every 6 months to review safety analyses. All efficacy and safety analyses will use a clinical data cutoff of 3 weeks before execution of the planned safety or interim analysis. This period will help ensure accuracy of the interim data by providing the sponsor time to perform data review, issue queries regarding data quality issues to sites, and to resolve such queries.

As per Section 9.1.2.2, the IRT system will use the number of responses and number of evaluable subjects in each cohort to perform the pooled PoS1 and PoS2 calculations for futility whenever a subject with endometrial, gastric, or head and neck cancer enters screening. To perform quality control checks of the futility analysis within the IRT system, the sponsor will review the disease response data within the IRT system for consistency with the clinical database and request changes to resolve discrepancies. There will be periodic data extracts to identify discrepancies between the IRT system and the clinical database.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 14.

Table 14: Statistical Analysis Plan Versions

SAP Version	Date
Original	05 DEC 2017

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf. Accessed January 4, 2016.

Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med 2008;27:3145-154.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

Simon R, Geyer S, Subramanian J, Roychowdhury S. The Bayesian basket design for genomic variant-driven phase II trials. Semin Oncol 2016;43:13-18.

APPENDIX A. PLANNED TABLES AND FIGURES

This appendix provides a list of the planned tables and figures for the Clinical Study Report. Standard tables will follow the conventions in the Standard Safety Tables initial version. Shells are provided for nonstandard tables in a separate document. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list of tables, figures, and the shells are to be used as guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard	In-Text
1.1 Baseline and Demographic Characteristics				
1.1	**Disposition**			
1.1.1.1	Analysis Populations	Phase 1 FAS Population	X	X
1.1.1.2	Analysis Populations	Phase 2 FAS Population	X	X
1.1.2.1	Summary of Subject Disposition	Phase 1 FAS Population	X	X
1.1.2.2	Summary of Subject Disposition	Phase 2 FAS Population	X	X
1.1.2.3	Summary of Subject Disposition	FAS Population	X	
1.1.3.1	Summary of Number of Subjects Enrolled by Country and Site	Phase 1 FAS Population	X	
1.1.3.2	Summary of Number of Subjects Enrolled by Country and Site	Phase 2 FAS Population	X	
1.2 Demography				
1.2.1	Summary of Demographics	Phase 1 FAS Population	X	X
1.2.2	Summary of Demographics - by Tumor Type	Phase 2 FAS Population	X	X
1.3 Baseline Characteristics				
1.3.1.1	Summary of Baseline Disease Characteristics and Disease History for Phase 1 Solid Tumor Types	Phase 1 FAS Population		
1.3.2.1	Summary of Baseline Disease Characteristics and Disease History for Phase 2 Solid Tumor Types	Phase 2 Biopsy FAS Population		
1.3.2.2	Summary of Baseline Disease Characteristics and Disease History	Phase 2 Endometrium FAS Population		
1.3.2.3	Summary of Baseline Disease Characteristics and Disease History	Phase 2 Gastric FAS Population		
1.3.2.4	Summary of Baseline Disease Characteristics and Disease History	Phase 2 SCCHN FAS Population		

Table No.	Title	Population	Standard	In-Text
1.4 Prior Medication and Concomitant Medication				
1.4.1.1	Summary of Prior Systemic Therapy	Phase 1 FAS Population		
1.4.1.2	Summary of Prior Systemic Therapy - by Tumor Type	Phase 2 FAS Population		
1.4.2.1	Summary of Prior Medications	Phase 1 FAS Population		
1.4.2.2	Summary of Prior Medications - by Tumor Type	Phase 2 FAS Population		
1.4.3.1	Summary of Concomitant Medications	Phase 1 FAS Population	X	
1.4.3.2	Summary of Concomitant Medications - by Tumor Type	Phase 2 FAS Population	X	
1.5 Others				
1.5.1	Summary of General Medical History	Phase 1 FAS Population	X	
1.5.2	Summary of General Medical History - by Tumor Type	Phase 2 FAS Population	X	
1.5.3	Summary of Protocol Deviations	FAS Population		
2 Efficacy				
2.1.1.1	Summary of Confirmed Best Response, Duration of Response, and Duration of Disease Control Under RECIST v1.1 - by Treatment Group and Tumor Type	Phase 2 Response Evaluable Population		X
2.1.1.2	Summary of Unconfirmed Best Response Under RECIST v1.1 - by Treatment Group and Tumor Type	Phase 2 Response Population		X
2.2.1	Summary of Unconfirmed Best Response, Duration of Response, and Duration of Disease Control Under RECIST v1.1 - by Treatment Group and Dose	Phase 1 Response Evaluable Population		X
2.2.2	Summary of Unconfirmed Best Response, Duration of Response, and Duration of Disease Control Under mRECIST v1.1 - by Treatment Group and Dose	Phase 1 Response Evaluable Population		X
2.2.3.1	Summary of Confirmed Best Response, Duration of Response, and Duration of Disease Control Under mRECIST v1.1 - by Treatment Group and Tumor Type	Phase 2 Response Evaluable Population		X
2.2.3.2	Summary of Unconfirmed Best Response Under mRECIST v1.1 - by Treatment Group and Tumor Type	Phase 2 Response Evaluable Population		X
2.4.1	Summary of Progression-Free Survival Under RECIST v1.1	Phase 1 FAS Population		X
2.4.2	Summary of Progression-Free Survival Under RECIST v1.1 - by Tumor Type	Phase 2 FAS Population		X
2.5.1	Summary of Progression-Free Survival Under mRECIST v1.1	Phase 1 FAS Population		X
2.5.2	Summary of Progression-Free Survival Under mRECIST v1.1 - by Tumor Type	Phase 2 FAS Population		X
2.6.1	Summary of Overall Survival	Phase 1 FAS Population		X
2.6.2	Summary of Overall Survival - by Tumor Type	Phase 2 FAS Population		X

Table No.	Title	Population	Standard	In-Text
[redacted]				
Safety				
3.1 Dose Exposure				
3.1.1.1	Summary of Drug Exposure to INCAGN01876 - by Treatment Group and Dose	Phase 1 FAS INCAGN01876 Population		X
3.1.1.2	Summary of Drug Exposure to INCAGN01876 - by Treatment Group and Tumor Type	Phase 2 FAS INCAGN01876 Population		X
3.1.2.1	Summary of Drug Exposure to Nivolumab - by Treatment Group and Dose	Phase 1 FAS Fixed Nivolumab Population		X
3.1.2.2	Summary of Drug Exposure to Nivolumab - by Treatment Group and Dose	Phase 1 FAS Weighted Nivolumab Population		X
3.1.2.3	Summary of Drug Exposure to Nivolumab - by Treatment Group and Tumor Type	Phase 2 FAS Fixed Nivolumab Population		X
3.1.2.4	Summary of Drug Exposure to Nivolumab - by Treatment Group and Tumor Type	Phase 2 FAS Weighted Nivolumab Population		X
3.1.3.1	Summary of Drug Exposure to Ipilimumab - by Treatment Group and Dose	Phase 1 FAS Ipilimumab Population		X
3.1.3.2	Summary of Drug Exposure to Ipilimumab - by Treatment Group and Tumor Type	Phase 2 FAS Ipilimumab Population		X
3.1.4.1	Summary of Drug Exposure to INCAGN01876 by Visit - by Treatment Group and Dose	Phase 1 FAS INCAGN01876 Population		
3.1.4.2	Summary of Drug Exposure to INCAGN01876 by Visit - by Treatment Group and Tumor Type	Phase 2 FAS INCAGN01876 Population		
3.1.5.1	Summary of Drug Exposure to Nivolumab by Visit - by Treatment Group and Dose	Phase 1 FAS Fixed Nivolumab Population		
3.1.5.2	Summary of Drug Exposure to Nivolumab by Visit - by Treatment Group and Dose	Phase 1 FAS Weighted Nivolumab Population		
3.1.5.3	Summary of Drug Exposure to Nivolumab by Visit - by Treatment Group and Tumor Type	Phase 2 FAS Fixed Nivolumab Population		

Table No.	Title	Population	Standard	In-Text
3.1.5.4	Summary of Drug Exposure to Nivolumab by Visit - by Treatment Group and Tumor Type	Phase 2 FAS Weighted Nivolumab Population		
3.1.6.1	Summary of Drug Exposure to Ipilimumab by Visit - by Treatment Group and Dose	Phase 1 FAS Ipilimumab Population		
3.1.6.2	Summary of Drug Exposure to Ipilimumab by Visit - by Treatment Group and Tumor Type	Phase 2 FAS Ipilimumab Population		
3.2 Adverse Events				
3.2.1.1	Overall Summary of Treatment-Emergent Adverse Events - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.2.1.2	Overall Summary of Treatment-Emergent Adverse Events - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.2.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.3.1	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.2.3.2	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.4.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.4.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.5.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.2.5.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.6.1	Summary of Any INCAGN01876 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.2.6.2	Summary of Any INCAGN01876 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.6.3	Summary of Any Nivolumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Nivolumab Population	X	X

Table No.	Title	Population	Standard	In-Text
3.2.6.4	Summary of Any Nivolumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Nivolumab Population	X	X
3.2.6.5	Summary of Any Ipilimumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Ipilimumab Population	X	X
3.2.6.6	Summary of Any Ipilimumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Ipilimumab Population	X	X
3.2.7.1	Summary of Any Grade 3 or Higher INCAGN01876 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.7.2	Summary of Any Grade 3 or Higher INCAGN01876 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.7.3	Summary of Any Grade 3 or Higher Nivolumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Nivolumab Population	X	
3.2.7.4	Summary of Any Grade 3 or Higher Nivolumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Nivolumab Population	X	
3.2.7.5	Summary of Any Grade 3 or Higher Ipilimumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Ipilimumab Population	X	
3.2.7.6	Summary of Any Grade 3 or Higher Ipilimumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Ipilimumab Population	X	
3.2.8.1	Summary of Any INCAGN01876 Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.8.2	Summary of Any INCAGN01876 Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.8.3	Summary of Any Nivolumab Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Nivolumab Population	X	
3.2.8.4	Summary of Any Nivolumab Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Nivolumab Population	X	

Table No.	Title	Population	Standard	In-Text
3.2.8.5	Summary of Any Ipilimumab Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Ipilimumab Population	X	
3.2.8.6	Summary of Any Ipilimumab Treatment-Related Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Ipilimumab Population	X	
3.2.9.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.9.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.10.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.2.10.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.11.1	Summary of INCAGN01876 Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.11.2	Summary of INCAGN01876 Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.11.3	Summary of Nivolumab Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.11.4	Summary of Nivolumab Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.11.5	Summary of Ipilimumab Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.11.6	Summary of Ipilimumab Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.12.1	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.12.2	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	

Table No.	Title	Population	Standard	In-Text
3.2.13.1	Summary of Treatment-Emergent Adverse Events Leading to INCAGN01876 Dose Reduction by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.13.2	Summary of Treatment-Emergent Adverse Events Leading to INCAGN01876 Dose Reduction by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.14.1	Summary of Treatment-Emergent Adverse Events Leading to Any Dose Interruption by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.14.2	Summary of Treatment-Emergent Adverse Events Leading to Any Dose Interruption by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.15.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCAGN01876 by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.15.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCAGN01876 by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.16.1	Summary of Treatment-Emergent Immune-Related Adverse Events (Investigator Identified) by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.16.2	Summary of Treatment-Emergent Immune-Related Adverse Events (Investigator Identified) by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.17.1	Summary of Treatment-Emergent Immune-Related Adverse Events (Sponsor Identified) by MedDRA System Organ Class and Preferred Term - by Treatment Group and Dose	Phase 1 FAS Population	X	
3.2.17.2	Summary of Treatment-Emergent Immune-Related Adverse Events (Sponsor Identified) by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
3.2.18.1	Summary of Treatment-Emergent Immune-Related Adverse Events (Investigator Identified) by MedDRA System Organ Class, Preferred Term, and Maximum Severity - by Treatment Group and Dose	Phase 1 FAS Population	X	
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Table No.	Title	Population	Standard	In-Text
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3.2.19.2	Summary of Grade 3 or Higher Treatment-Emergent Immune-Related Adverse Events (Investigator Identified) by MedDRA System Organ Class and Preferred Term - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X
3.2.20	Life Table Estimate of Time to First Grade 3 or Higher Treatment-Emergent Adverse Event - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	
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3.3.2.1	Summary of Treatment Emergent Worsening Hematology Laboratory Values in CTC Grade - To the Worst Abnormal Value	Phase 1 FAS Population	X	
3.3.2.2	Summary of Treatment Emergent Worsening Hematology Laboratory Values in CTC Grade - To the Worst Abnormal Value	Phase 2 FAS Population	X	
3.3.3	Summary of Laboratory Values - Chemistry	Phase 2 FAS Population	X	
3.3.4.1	Summary of Treatment Emergent Worsening Chemistry Laboratory Values in CTC Grade - To the Worst Abnormal Value	Phase 1 FAS Population	X	
3.3.4.2	Summary of Treatment Emergent Worsening Chemistry Laboratory Values in CTC Grade - To the Worst Abnormal Value	Phase 2 FAS Population	X	
3.4 Vital Signs				
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3.4.1.2	Summary of Systolic Blood Pressure (mmHg) - by Tumor Type	Phase 2 FAS Population	X	
3.4.2.1	Summary of Diastolic Blood Pressure (mmHg)	Phase 1 FAS Population	X	
3.4.2.2	Summary of Diastolic Blood Pressure (mmHg) - by Tumor Type	Phase 2 FAS Population	X	
3.4.3.1	Summary of Pulse (bpm)	Phase 1 FAS Population	X	

Table No.	Title	Population	Standard	In-Text
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3.4.4.2	Summary of Respiration Rate (bpm) - by Tumor Type	Phase 2 FAS Population	X	
3.4.5.1	Summary of Body Temperature (°C)	Phase 1 FAS Population	X	
3.4.5.2	Summary of Body Temperature (°C) - by Tumor Type	Phase 2 FAS Population	X	
3.4.6.1	Summary of Weight (kg)	Phase 1 FAS Population	X	
3.4.6.2	Summary of Weight (kg) - by Tumor Type	Phase 2 FAS Population	X	
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3.5.1.1	Summary of PR Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.1.2	Summary of PR Interval (msec) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	
3.5.2.1	Summary of RR Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.2.2	Summary of RR Interval (msec) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	
3.5.3.1	Summary of QT Interval (msec) From Local l Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.3.2	Summary of QT Interval (msec) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	
3.5.4.1	Summary of QRS Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.4.2	Summary of QRS Interval (msec) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	
3.5.5.1	Summary of QTcB Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.5.2	Summary of QTcB Interval (msec) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	
3.5.6.1	Summary of QTcF Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.6.2	Summary of QTcF Interval (msec) From Local Lab 12-Lead ECG- by Tumor Type	Phase 2 FAS Population	X	
3.5.7.1	Summary of JTc Interval (msec) From Local Lab 12-Lead ECG	Phase 1 FAS Population		
3.5.7.2	Summary of JTc Interval (msec) From Local Lab 12-Lead ECG- by Tumor Type	Phase 2 FAS Population	X	
3.5.8.1	Summary of Heart Rate (beats/min) From Local Lab 12-Lead ECG	Phase 1 FAS Population	X	
3.5.8.2	Summary of Heart Rate (beats/min) From Local Lab 12-Lead ECG - by Tumor Type	Phase 2 FAS Population	X	

Table No.	Title	Population	Standard	In-Text
3.5.9.1	Summary of Alert Values of PR, QRS, QT, RR, and QTcF Interval Values From Local Lab 12-Lead ECG by Visit - by Treatment Group and Dose	Phase 1 FAS Population	X	X
3.5.9.2	Summary of Alert Values of PR, QRS, QT, RR, and QTcF Interval Values From Local Lab 12-Lead ECG by Visit - by Treatment Group and Tumor Type	Phase 2 FAS Population	X	X

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Figure No.	Title	Population
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40.90.2.1	Line Graph of Selected Laboratory Values by Study Visit	Phase 1 FAS Population
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40.90.3.1	Box-and-Whisker Plot of Selected Laboratory Values by Study Visit	Phase 1 FAS Population
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APPENDIX B. TECHNICAL REPORT FOR INTEGRATED BAYESIAN FUTILITY ANALYSIS

Introduction

In this document, we present a strategy for pooling information across the tumor types and sequencing strategies defined in Section 3. The strategy is based on Simon et al (2016). The Bayesian pooling strategy will be used to carry out interim futility analyses and end-of-study efficacy analyses for each cohort. We begin with an introduction to the overall study design, and then we present simulation results and operating characteristics that illustrate the application of the Simon et al (2016) method in Part 2 of this study.

Phase 2 of the study will evaluate the efficacy of the recommended dose of INCAGN01876 as part of a doublet combination with the approved immunotherapy nivolumab and as part of a triplet combination with the approved immunotherapies nivolumab and ipilimumab. Subjects with endometrial, gastric, and SCCHN tumors will be evaluated in each of the doublet and triplet combinations. In addition, each of the doublet and triplet combinations will be tested using 3 dose-sequencing strategies: concurrent dosing of INCAGN01876 and immunotherapy, INCAGN01876 run-in Q2W for 2 doses followed by immunotherapy, and INCAGN01876 run-in Q2W for 2 doses followed by concurrent dosing of INCAGN01876 and immunotherapy.

In total, the study design for Phase 2 will test 18 unique tumor type (within doublet or triplet) and sequencing strategy cohorts. Each of the 18 cohorts will be evaluated by Simon 2-Stage design (Simon 1989). All sequencing strategies for a particular tumor type and doublet or triplet combination will use the same Simon 2-Stage design.

Table 12 shows the dose sequencing strategy and tumor type–specific strategy for each of the 18 cohorts used for pooling in the integrated Bayesian analysis. It is believed that activity or the lack of activity within any of the tumor types in a particular sequencing strategy will provide information about the activity in other tumor types in that sequencing strategy. It is also believed that activity or the lack of activity in 1 of the sequences tested on a specific tumor type will provide information about the activity in the other sequences tested on the same tumor type.

For the analysis within sequencing strategies, there will be 6 strata within each sequencing strategy. For the analysis within tumor types, there will be 3 strata within each tumor type.

Parameters to be specified a priori include λ, the probability of homogeneity, which controls the amount of borrowing; γ, the probability of activity in any stratum; and a vector of probabilities of length k equal to the number of strata, specifying individual probabilities of success in each stratum when the strata are not homogeneous, $\Pr[p = q]$. Here, the p vector represents the probability of activity in each stratum, and q is the outcome vector for p, each entry of q is p_1 or p_0, corresponding to the probabilities of activity or inactivity, respectively, in the individual strata. This leads to 2^k possibilities for the $\Pr[p = q]$ vector. The individual p_1 vectors are the target response rates from the Simon 2-Stage design for the given tumor types, and the individual p_0 vectors are the unacceptable response rates from the same Simon 2-Stage designs. To clarify, the $\Pr[p = q]$ vector is used in the calculation of the likelihood, but not in the calculation of the prior PoS.

To calculate prior PoS in any given cohort, we first determine all 2^k permutations of successes and failures among the k cohorts and store these permutations in a matrix, m. Below is an example of the 8×3 m matrix for 3 strata. The rows of the m matrix represent the permutations, the columns represent the cohorts, and each entry in a row of 1 or 0 represents success or failure, respectively, for that cohort in the corresponding permutation.

$$m = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 1 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix}$$

For rows 2 through 2^k-1 of the permutation matrix, where i represents the ith row and j represents the jth column, the prior PoS is defined as follows:

$$\text{PoS} = (1-\lambda) \times \gamma^{\sum_{i=1}^{2^k} m_{ij}} (1-\gamma)^{\sum_{i=1}^{2^k} 1-m_{ij}},$$

where $1-\lambda$ is the probability that the cohorts are independent; γ is the probability of activity; $\sum_{i=1}^{2^k} m_{ij}$ is the sum of the number of active cohorts under all permutations; $1-\gamma$ is the probability of inactivity; and $\sum_{i=1}^{2^k} 1-m_{ij}$ is the sum of the number of inactive cohorts under all permutations.

For row 1, which represents the case in which all cohorts are inactive, we add in the probability that the cohorts are correlated times the probability of inactivity:

$$\text{PoS} = (1-\lambda) \times \gamma^{\sum_{i=1}^{2^k} m_{ij}} (1-\gamma)^{\sum_{i=1}^{2^k} 1-m_{ij}} + \lambda(1-\gamma).$$

For row 2^k, which represents the case in which all cohorts are active, we add in the probability that the cohorts are correlated times the probability of activity:

$$\text{PoS} = (1-\lambda) \times \gamma^{\sum_{i=1}^{2^k} m_{ij}} (1-\gamma)^{\sum_{i=1}^{2^k} 1-m_{ij}} + \lambda\gamma.$$

Posterior PoS calculations based on sharing within the tumor types and within the sequencing strategies will be updated each time a subject with the tumor type of interest enrolls in the study using data already collected from subjects already on the study.

The posterior probabilities depend on the number of responses and sample sizes in each of the strata at the time, denoted by the vectors r and n respectively. The posterior PoS in tumor type i and sequence strategy j is proportional to the prior probability times the likelihood of the response data observed up to that point if the response numbers are given by the r vector, if the sample sizes are given by the n vector, and if q_{ij} is p_1 times the same likelihood of the response data observed up to that point q_{ij} is p_0:

$$PoS = \Pr(\boldsymbol{p} = \boldsymbol{q}|\lambda, \gamma, \boldsymbol{r}, \boldsymbol{n})$$
$$= \left((1-\lambda) \times \gamma^{\sum_{i=1}^{2^k} m_{ij}} (1-\gamma)^{\sum_{i=1}^{2^k} 1-m_{ij}}\right)$$
$$\times \prod_i \prod_{j, q_{ij}=p_1} {q_{ij}}^{r_{ij}} (1-q_{ij})^{n_{ij}-r_{ij}} \times \prod_i \prod_{j, q_{ij}=p_0} {q_{ij}}^{r_{ij}} (1-q_{ij})^{n_{ij}-r_{ij}}$$

As an example of the PoS calculation, we look at a simplified example with 3 strata in Table B1. Suppose that we observe the following results for the evaluable subjects in a study with 3 separate Simon 2-Stage designs with target rates of 0.25 and unacceptable rates of 0.05. The optimal Simon 2-Stage design with these criteria has an interim sample size of 19, total sample size of 55, $r = 3, r = 12$. The PoS calculation for each controls the degree of sharing of data between the strata and γ as the prior probability of activity for a given cohort. Note that the parameter λ has a direct relationship with the calculated PoS value across the 3 stratum.

Table B1: Example PoS Calculations for 3 Stratum

Stratum	**1**	**2**	**3**
Responders/evaluable subjects	6/20	3/10	1/5
PoS based on λ = 0.5 and γ = 0.33	0.99	0.98	0.90
PoS based on λ = 0.05 and γ = 0.33	0.99	0.93	0.18

For the purposes of this analysis, we will specify a single value for λ and γ, so that the rate of sharing within sequences and tumor types will be equal, and the prior PoS assumed within strata in the pooling strategies will be equal. The PoS in tumor type (tumor type i and sequencing strategy j) will be denoted by $PoS1_{ij}$, and the PoS within sequencing strategy (tumor type i and sequencing strategy j) will be denoted by $PoS2_{ij}$.

Based on the results of the 2 calculated posterior PoS values, a tumor-sequence pair (i,j) will be considered open for randomization if either $PoS1_{ij}$ or $PoS2_{ij}$ is greater than 20%. Otherwise, the tumor-sequence pair will be suspended with the possibility of being re-opened after more data have accrued and subsequent posterior PoS values are greater than 20% for the tumor-sequence pair.

At the end of the study, overall PoS tests will be performed using both $PoS1_{ij}$ and $PoS2_{ij}$. A tumor-sequence strategy will be considered successful at the end of the study if either $PoS1_{ij}$ or $PoS2_{ij} > 80\%$.

Each time a subject with the tumor type of interest is enrolled, 2 PoS calculations will be performed using the evaluable subjects: the PoS in tumor type (tumor type i and sequencing strategy j), $PoS1_{ij}$, and PoS within sequencing strategy (tumor type i and sequencing strategy j), $PoS2_{ij}$.

Simulations and Operating Characteristics

Computer simulations were conducted in R to compare the operating characteristics of the Bayesian basket trial design with the operating characteristics of 18 separate Simon 2-Stage designs. We investigated 6 scenarios that would represent different configurations of null and alternative hypotheses (corresponding to inactivity of drug and activity of drug) within the sequencing strategies and tumor types. For the global null hypothesis of no activity in any cohort (Scenario 1), 2500 replications were performed. All other scenario results were simulated using 1000 replications.

In the computer simulations, we assumed the prior probability of correlation between cohorts within tumor types and sequencing strategies to be $\lambda = 0.4$ and prior probability of activity to be $\gamma = 0.4$.

The Simon 2-Stage designs used in the simulations are given in Table 2. The p_1 and p_0 values are assumed not to change with sequencing strategy. For example, for each of the 3 sequencing strategies tested on the SCCHN doublet, $p_1 = 0.35$ and $p_0 = 0.15$. The total sample sizes if each cohort reached full enrollment are given by the n column in Table 2.

Within the simulations, a tumor-sequence pair (i, j) was stopped if neither $PoS1_{ij}$ nor $PoS2_{ij}$ was ≥ 20% at any point. In addition, the first stage rule for the Simon 2-stage design was also applied where enrollment was halted unless more than r_1 of the first n_1 subjects responded to treatment within a tumor-sequence pair. The method rejected the null hypothesis of no activity in a cohort at the end of the study if either $PoS1_{ij}$ or $PoS2_{ij}$ > 80%.

For purposes of the simulation, tumor responses were programmed to occur 16 weeks after start of treatment. A 7-month period was assumed between the opening of the doublet and triplet tumor type cohorts. During the first 7 months, subjects were equally distributed among endometrial, gastric, and SCCHN tumor types and subjects of each tumor type were randomly assigned to the 3 sequence strategies. After the first 7 months, the triplet tumor type cohorts opened, subjects were still equally distributed among endometrial, gastric, and SCCHN tumor types and were sequentially assigned to the doublet and triplet sequencing strategy–specific treatment groups that were available after the interim futility and Simon 2-Stage futility rules were applied. Enrollment in each tumor type was assumed to occur over a 33-month period with subjects equally distributed between the 3 tumor types over that period and rates of enrollment increasing over the length of enrollment. Enrollment was generated by an exponential(0.7) curve. Projected maximum enrollment by quarter is defined in Table B2.

Table B2: Simulated Enrollment by Quarter-Year From Trial Start

Quarter #	**1**	**2**	**3**	**4**	**5**	**6**
Enrollment	28	76	136	207	284	369
Quarter #	**7**	**8**	**9**	**10**	**11**	
Enrollment	460	557	658	766	873	

The operating characteristics obtained from the simulations are given in Table B3. Compared against 18 separate Simon 2-Stage designs, the Bayesian basket trial offers a significant reduction in sample size and close to 10% Type I error control. The individual Simon 2-Stage designs are considered to be independent trials and would offer no attempt to control Type I error. The Bayesian basket trial also offers high power (in most cases more than 97%) to reject the null hypotheses of no activity in the cohorts when activity is present. In Scenario 6, when only 1 of the 18 cohorts has activity, the Bayesian basket trial still has 63.7% power to reject the null hypothesis for that cohort.

Table B3: Operating Characteristics Based on Simulation Results

Scenario	Expected Sample Size	Probability of a Single False Positive Result	Expected Number of False Positive Results	Power to Reject ≥ 1 True Alternative Hypothesis	Expected Number of True Rejections	Number of True Alternative Hypotheses	Expected Sample Size for Simon 2-Stage Design	Expected Number of Correct Rejections for Simon 2-Stage Design	Expected Number of False Rejections for Simon 2-Stage Design
Global null hypothesis	355.2	0.0876	0.104	–	–	0	457.2	–	0.9
Global alternative hypothesis	807.0	–	–	> 0.999	16.3	18	807.7	15.3	–
Alternative hypotheses in Tumor Type 1, null for Tumor Types 2 and 3	534.8	0.135	0.153	> 0.999	5.0	6	574.7	5.1	0.6
Alternative hypothesis in Sequence 1, null for Sequences 2 and 3	527.9	0.150	0.162	> 0.999	5.4	6	574.0	5.1	0.6
Alternative hypothesis in Tumor Type 1 in triplet, all others null	444.5	0.127	0.139	0.978	2.5	3	515.7	2.55	0.75
Alternative hypothesis in Tumor Type 1 in triplet Sequence 1, all others null	387.7	0.123	0.136	0.637	0.6	1	476.7	0.85	0.85